



# Application of Oxytocin in HIFU Treatment of Uterine Fibroids

In this lecture we are going to learn the application of oxytocin in HIFU treatment of uterine fibroids.

HIFU ablation of uterine fibroids started around the year of 2000 with the first article published by Prof. WANG Wei from Chinese PLA General Hospital. In the exploratory stage, both epidural and general anaesthesia were used, instead of the uniform sedation and analgesia that we use now. General anaesthesia-induced neuronal blockade resulted in a relatively high rate of neuronal and postoperative complications. Thus, HIFU ablation of uterine fibroid did not seem so promising back then.

In 2006, we investigated the feasibility of performing HIFU under sedation and analgesia. It was found to be a more effective and safer method that can maximally protect nerve function intact. Hoping to shorten treatment time under sedation and analgesia, the application of oxytocin was introduced, optimized and finally has become part of the treatment protocol.

## I. About Oxytocin

Clinical application of oxytocin has a long history. It works by binding to the oxytocin receptor on the plasma membrane of the uterine smooth muscle cells and concentrating intracellular calcium, causing the contraction of uterine smooth muscles. Compression of the blood vessels by the muscle contraction results in the reduction of the uterine perfused volume. Oxytocin can act on both pregnant and non-pregnant uterus, while the former is more sensitive because it has more oxytocin receptors.

The effectiveness of oxytocin in reducing the perfused volume in targeted uterine lesion has provided a more efficient and time-saving way of performing HIFU ablation.



Based on our clinical experience and research data, the effect of oxytocin is more pronounced in HIFU ablation of uterine fibroids than in adenomyosis.

## **II. Studies in the feasibility of using Oxytocin in HIFU ablation of uterine fibroids**

Before adding oxytocin to HIFU ablation protocol, we conducted feasibility studies.

The first published study included 26 patients bearing 29 fibroids. Since it was not clear at the time of the study whether HIFU ablation might negatively impact fertility function of the ovaries, all patients included were without pregnancy desire and with a mean age of around 40 years. In the early stage of the researches, because we had no idea about the influence of HIFU treatment of uterine fibroids on the fertility of patients, patients without pregnancy desire were mostly admitted for HIFU treatment, the size of fibroids were all over 5 cm, which met the surgical criteria for the time being. HIFU treatment was performed under MRI guidance. The dose of oxytocin was 0.32 U / min, i.e. 80 units of oxytocin prepared in 500 ml of 5% glucose solution. The rationale for choosing a higher dose of oxytocin than the usual used for pregnant uterus was based on the published studies showing less responsiveness of the non-pregnant uterus to Oxytocin.

This is the transducer, there is a water balloon in the middle. This is a snapshot of MRI monitoring during HIFU ablation (T1WI). Different colors represent different temperature. Red represents the targeted lesions, where the temperature is the highest, exceeding 52 degrees. Other colors indicate the temperature is below 52 degrees. Away from the focus, a sharp drop of temperature could be observed.

Why do we design temperature mapping this way? In a cytological view, cells undergo irreversible coagulative necrosis when the temperature exceeds 52 degrees; while the damage to the cells is reversible if the temperature is between 43 degrees and 52 degrees. Red color indicates the achievement of the desirable treatment effect. When the entire fibroid is covered by red dots, successful ablation is achieved.

Nowadays, we mainly use ultrasound-guided HIFU equipment for the treatment. Compared with MR-guided HIFU equipment, the former is better in real-time and treatment time-saving. The treatment effect of ultrasound-guided HIFU is evaluated based on the gray-scale changes in ultrasound images.

Here we can see significant changes in the ultrasound energy consumed for ablation and sonication time before and after using oxytocin. It is obvious that oxytocin is helpful.

We analyzed the effect of T2 signal on oxytocin response and found better response in fibroids that have hyperintense signals on T2WI. Fibroids with hyperintense signals on T2WI are hard to achieve complete ablation without the help of oxytocin, usually 50% ablation is acceptable, and 70% ablation is rarely attainable.

This study concludes that oxytocin can significantly decrease the energy required for ablation, shorten treatment time and improve treatment efficiency.

In the second study, we measured the blood vessels with an ultrasound scan before and after using oxytocin. In different dosage groups, we observed the differences in peak systolic velocity, diameter of vessels and resistance index.

In conclusion, both the mean velocity of blood flow and the diameter of vessels significantly changed after infusion of oxytocin. The perfused volume reduced by around 80%.

These images reveal that the perfused volume both surrounding and inside the fibroids decreased after intravenous infusion of oxytocin. The blood flow reduction inside fibroid was more pronounced. Because the intratumoral blood vessels are thinner and are easier to be compressed and contract.

We can see the mean velocity of blood flow inside the fibroid reduced from 14 to 3, and the change in the diameters of vessels was also obvious. The perfused volume reduced by approximately 90%.

This graph illustrates the relation between the change of blood flow surrounding and inside the fibroid and the dosage of oxytocin. Although the curve goes relatively flat.



The test result indicates that intravenous infusion of oxytocin can effectively reduce the vascularity of fibroids. The smallest dose of 0.12U / min, around 20 units of oxytocin, equivalent to the dosage we normally use in obstetrics appears sufficient in this case.

### III. Oxytocin test

Based on the above findings and experience, we proposed oxytocin tests before HIFU treatment.

To provide a guide for HIFU treatment planning, to determine efficacy of HIFU treatment, to facilitate a more effective doctor-patient communication

Oxytocin test is required in one of the following cases: 1. hypervascular fibroids are confirmative (grade III or higher on CDFI); 2. the peak systolic velocities of blood flow surrounding and inside the fibroid are over 40 cm / s; 3. the fibroids are visualized as isointense signals on T2WI and significant contrast enhancement on T1WI.

Let's look at an example. This is a case where an oxytocin test is required. Because fibroids of hyperintense signals on T2WI have more water, indicating the possibility of mucoid degeneration, liquefaction or steatosis. It's more difficult to deal with. The more significant the contrast enhancement is (or the lesion presents brighter than normal myometrium), the more difficult the treatment may be.

For instance, the signals of fibroid on T2WI appears brighter than that of normal myometrium, indicating hyper-intense signals; if they are similar to that of myometrium but brighter than that of skeletal muscle, it indicates iso-intense signals. Hyperintense signal cases are difficult to treat. It would be demanding to achieve an ablation rate of 50%. We will come back to this case later.

For oxytocin test, we now recommend 40 units of oxytocin in most cases and 20 units will do in some cases. In our experience, we administrate larger doses, as high as 120 units in order to cover all the oxytocin receptors, as the patients we treat are non-pregnant. Then the peak systolic velocity of blood flow and the artery diameter will be measured. The mean velocity of three big blood vessels inside the fibroid will also be



measured if time permits. If time presses, the mean velocity will be estimated based on the blood flow velocity of one big vessel.

Give oxytocin (dose: 0.12 U /min) through intravenous infusion at the rate of 30 drops per minute.

Measure the diameter of the peripheral artery, the diameter of internal artery, and the blood flow parameters at 5min, 10min, and 20min after administration.

If the reduction of blood perfusion is not satisfactory, increase the dose of oxytocin solution to 0.24 U/min (80 U of oxytocin + 500 ml of 5% glucose solution) and then continue to observe the patient's response.

If the reduction of blood perfusion is still not satisfactory, then increase the dose of oxytocin solution to 0.36 U /min (120 U of oxytocin + 500 ml of 5% glucose solution).

Observe the vital signs of the patient during the whole treatment process. If any adverse event happens, manage it immediately.

To examine the change in uterine vascularity with ultrasound scan, the parameter setting of the ultrasound scanner should be kept consistent.

Then the perfused volume of blood vessel will be calculated, using the equation  $Q = \pi r^2 \cdot V$ , where  $V$  is the mean velocity of blood flow.

The perfused volume before infusion of oxytocin ( $Q_1$ ) subtracts the perfused volume after infusion of oxytocin ( $Q_2$ ), and then is divided by  $Q_1$  and multiplied by 100%, yielding reduction rate of perfused volume.

Usually the test lasts for 5 minutes for the sake of safety and efficacy. If the change of perfused volume is not obvious after 5 minutes, we will prolong the time or increase the concentration of oxytocin.

Through the changes in the blood flow surrounding and inside fibroid, we can predict the test outcome. Fibroids that have reduction in the blood flow surrounding the fibroid less than 50% are insensitive to oxytocin thus HIFU ablation is not recommended.



Fibroids that have reduction in intratumoral blood flow more than 50% but less than 75% are moderately sensitive to oxytocin. The result of HIFU ablation may be not ideal. In such case, we need to inform the patients of the likelihood of undesirable outcome and leave decision to the patients. Fibroids that have reduction in intratumoral blood flow exceeds 75% are sensitive to oxytocin and favorable outcome is predicted. HIFU ablation will be recommended to the patients.

Let's look at the ultrasound images before and after using oxytocin. Calculation was not necessary, as the blood flow changes were obvious. We can observe significant reduction in the blood flow surrounding fibroid, indicating high sensitivity to oxytocin.

In another scenario, we may detect thick blood vessels upon oxytocin infusion. Our previous animal experiments show that the blood vessel bigger than 2 mm in diameter cannot be ablated by ultrasound.

However, some large uterine fibroids with big vessels can still be ablated. This is because, firstly, the blood vessel will shrink to smaller than 2 mm after administration of oxytocin. Secondly, intensified treatment intensity can ablate the tissue around the big vessel, after which the big vessel inside will also shrink.

Comparing the right side image captured before using oxytocin and the left side image captured after using oxytocin, while we found remaining blood vessels inside the fibroid, the blood flow significantly decreased. Thus this fibroid was responsive to oxytocin.

These are the MRIs of the patient mentioned. The left side and the right side images were captured before and after using oxytocin respectively. Below are the relevant parameters of the blood vessels before and after using oxytocin, including the internal diameter of arteries, the systolic blood flow velocity, and the diastolic blood flow velocity. Reduction in perfused volume is 61%, indicating sensitivity to oxytocin, but not sufficient. .



For this patient, the reduction in perfused volume was over 50% but lower than 75%. In this case, we need to inform the patient that the ablation result may be not desirable or the procedure may be risky, and leave the choice to the patient.

Intensified treatment may bring about better treatment effect for this kind of fibroids but in the meantime is associated with a higher risk of skin burns. So the treatment needs to be conducted by an experienced specialist.

In most cases, the treatment intensity is 1-second sonication and 3-second rest. If the patient's tolerance permits, we can increase the treatment intensity gradually to 2-second sonication and 4-second rest, while 2-second sonication and 3-second rest is the upper limit for most patients. For this patient, we used very high intensity 3:5, that is 3-second sonication and 5-second rest.

On this patient, we increased the intensity to 3-second sonication followed by a 5-second rest, because the patient's tolerance was good. The lumped gray-scale changes appeared after 1300-second sonication. The treatment intensity was so high, causing swelling of the rectus abdominis. Post-treatment MRIs show the rectus abdominis was thicker than normal one.

What is good is that the ablation rate was desirable over 70%, though with some unablated vessels at the edge of the lesion, which might lead to relapse.

Why was the patient willing to choose HIFU? The patient was then only 27 years old and had no history of pregnancy. Unwilling to receive open surgery, which would cause a trauma to uterus, the patient chose noninvasive HIFU treatment. Even if the treatment effect of HIFU were not desirable, she could still undergo open surgery afterwards. Most patients with fibroid(s) of hyperintense T2 signals are young, aged less than 35 years old. For these patients, regular post-treatment examinations at an interval of 3 months are recommended, especially in the first half year after treatment.

In one of the cases we have treated, though 90% of the fibroid was ablated and absorbed afterwards, the rest of the 10% unablated lesion at the edge of fibroid regrew within a half year after treatment. For this patient, we chose to perform second HIFU ablation when significant shrinkage of the fibroid was achieved. Since the blood vessels



surrounding the fibroid had shrunk along with the shrinkage of the ablated lesion, higher ablation rate was achieved.

For such fibroid(s) likely to relapse, i.e. fibroids with rich blood supply and visualized as hyper-intense signals on T2WI, it is important to seize the time window for performing the second treatment and to discuss with the patient before the first treatment the possibility of relapse and the need of reintervention. If we seize the time window for reintervention, the ablation outcome will be better with lower possibility of recurrence. Fibroids, ablated 100%, will not relapse.

Though oxytocin is generally safe, it has some side effects recorded in obstetrics. Side effects such as dizziness, chest tightness, chills and fever have not been observed when it is used for HIFU ablation. This may have to do with the relatively good physique of our non-pregnant patients aged from 20 to 50 years old.

The major adverse effect of oxytocin we have encountered is on the cardiovascular system. We found that some patients had transient heart rate acceleration at the start of oxytocin infusion but it quickly returned to normal. While the primary function of oxytocin is to cause vessel contraction, when administrated at large dosage, it may work reversely, resulting in a temporal drop in blood pressure. This may happen but is rare. Thus we generally recommend 40 units of oxytocin for HIFU ablation. The 20 units dosage used in obstetrics is sufficient in the case of fibroids of hypointense T2 signals.

Another adverse effect is suppression of urine excretion, which may lead to hyponatremia (a condition where the concentration of sodium in blood is abnormally low) during fluid infusion, or more seriously cause water intoxication and pulmonary edema. However it is very rare.

In clinical practice, oxytocin is found to be compatible with HIFU ablation procedure as oxytocin can maintain contraction of uterine vessels for 1 hour to 1.5 hours. However, for gynecological surgery, instead of oxytocin, pituitrin and other drugs alike are more often used to reduce post-operative bleeding. Therefore, we evaluated the feasibility of using these agents for HIFU ablation and discovered their limitations. For example, the duration of pituitrin effect is brief and it has profound effect on





hemodynamics. We encountered a patient undergoing open surgery, whose blood pressure surged from 120 to 220 after using pituitrin. It was a very dangerous situation.

#### **IV. Alternative drugs**

We have also conducted clinical studies on the application of ergometrine in HIFU ablation. We found that while intravenous administration of ergometrine had no significant effect on uterine blood supply, it had a strong effect on peripheral vessels. Within 5 min after intravenous infusion of ergometrine, the contraction of peripheral veins prevented the fluid from entering the peripheral vessels.

In some cases, local or combined use of multiple agents may be applied with the aim of enhancing vessel contraction. However, oxytocin remains our primary choice.

In today's lecture, the take home key point is the oxytocin test. If you have difficulties in selecting cases suitable for HIFU ablation, you are strongly encouraged to contact our specialists. We also encourage you learn by doing and gain insights from your own clinical experience. You are more than welcome to contact us at any time.